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(54) Title: SYNERGISTIC ANTIMICROBIAL, DERMATOLOGICAL AND OPHTHALMIC PREPARATIONS CONTAINING CHLORITE AND HYDROGEN PEROXIDE

(57) Abstract

Antimicrobial/pharmaceutical preparations (e.g., solutions, gels, ointments, creams, sustained release preparations, etc.) which include chlorite (e.g., a metal salt of a chlorite) in combination with a peroxy compound (e.g., hydrogen peroxide), and methods for using such preparations for disinfection of articles or surfaces (e.g., contact lenses, counter tops, etc.), antisepsis of skin or other body parts, prevention or deterrence of scar formation and/or treatment and prophylaxis of dermal (i.e., skin or mucous membrane) disorders (e.g., wounds, burns, infections, cold sores, ulcerations, psoriasis, acne, or other scar–forming lesions).

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SYNERGISTIC ANTIMICROBIAL, DERMATOLOGICAL AND OPHTHALMIC PREPARATIONS CONTAINING CHLORITE AND HYDROGEN PEROXIDE

Field of The Invention

The present invention relates generally to medical compositions and methods, and more particularly to certain disinfectant/antimicrobial preparations and methods for using such preparations i) to disinfect or preserve articles or surfaces, ii) as a topical antiseptic for application to body parts, iii) to prevent or deter scar formation; iv) to treat dermatological disorders such as wounds, burns, ulcers, psoriasis, acne and other scar forming lesions; and v) to treat ophthalmic disorders such as dry eye, wound healing, and allergic conjunctivities.

Background of the Invention

A. Antimicrobial and Disinfectant/Antiseptic Agents Used for Disinfection/Antisepsis and Topical Treatment of Wounds, Burns, Abrasions and Infections

The prior art has included numerous antimicrobial agents which have purportedly been useable for disinfection of various articles and/or for topical application to a living being for antisepsis and/or treatment of dermal disorders (e.g., wounds, burns, abrasions, infections) wherein it is desirable to prevent or deter microbial growth to aid in healing. Such topical antimicrobial agents have contained a variety of active microbicidal ingredients such as iodine, mercurochrome, hydrogen peroxide, and chlorine dioxide.

i. Prior Chlorine Dioxide Preparations

Chlorite, a precursor of chlorine dioxide, is known to be useable as a disinfectant for drinking water and as a preservative for contact lens care solutions. However, chlorite exhibits only weak microbicidal activity within a concentration range that is acceptable and safe for

topical application to the skin (e.g., 50-1000 parts per million). Thus, chlorite has not been routinely used as an active microbicidal ingredient in preparations for topical application to the skin.

In view of the limited usefulness of chlorite as an antiseptic or topical microbicide, various compositions and methods have been proposed for activation or enhancement of the microbicidal activity of chlorite. Examples of such compositions and methods for activation or enhancement of the microbicidal activity of chlorite are described in United States Patent Nos. 4,997,616 (describing general activation); 5,279,673 (describing acid activation) and 5,246,662 (describing transitional metal activation).

Chlorine dioxide (ClO_2) and "stabilized chlorine dioxide" are known to be useable as antiseptics. Chemically, chlorine dioxide is an oxidizing agent which has strong microbicidal activity. Chlorine dioxide is generally regarded as superior even to gaseous chlorine, in certain water treatment applications where it is used as to eliminate algae and other organic material and/or to remove odors or tastes. Chlorine dioxide is also effective as a microbicide, for elimination of bacteria, viruses, and microbial spores.

In addition to its use as a microbicide, chlorine dioxide is a highly reactive, unstable radical which is useable as an oxidizing agent in a number of other chemical and biochemical applications. For example, as described in United States Patent No. 4,855,135, chlorine dioxide can be used for (a) oxidation of double bonds between two carbon atoms; (b) oxidation of unsaturated fatty acids (lipids) via double bonds between two carbon atoms; (c) acceleration of hydrolysis of carboxylic anhydrides; (d) oxidation of aldehydes to the corresponding carboxylic acids; (e) oxidation of alcohols; (f) oxidation of amines; (g) oxidation of phenols, phenolic derivatives and thiophenolic compounds;

(h) moderate oxidation of hydroquinones; (i) oxidation of amino acids, proteins and polyamides; j) oxidation of nitrates and sulphides; and (k) alteration of the CHO and CH_2OH radicals of carbohydrates to produce carboxylic functionality.

Concentrated chlorine dioxide in its liquid or gaseous state is highly explosive and poisonous. As a result, concentrated chlorine dioxide must be handled and transported with great caution. For this reason, it is generally not feasible to dispense pure chlorine dioxide for use as a topical antimicrobial agent or disinfectant. Instead, same antimicrobial or disinfectant preparations have been formulated to provide for "acid generation" of chlorine dioxide. Such acid generation solutions contain a metal chlorite (i.e., a precursor of chlorine dioxide available in powdered or liquid form) in combination with an acid which will react with the chlorite to liberate or release chlorine dioxide. Generally, any acid may be used for acid generation of chlorine dioxide, including strong acids such as hydrochloric acid and sulfuric acid and relatively weak acids such as citric and tartaric acid. Drawbacks or problems associated with these prior chlorine dioxide generating systems include a) the inconvenience of handing two separate containers or chemical components, b) the difficulty of delivering such two-component systems to the intended site of application, and c) the fact that these prior systems are of acid, rather than neutral, pH. Moreover, the prior chlorine dioxide generating systems which utilize acid-induced generation of chlorine dioxide can, if uncontrolled, cause the generation of chlorine dioxide to occur quite rapidly and, as a result, the disinfectant or antimicrobial potency of the solution may be short lived. Increasing the concentration of chlorite and acid within the solution may prolong its disinfectant or antimicrobial shelf life, but such increased concentrations of these chemicals can result in

toxicities or (in topical applications) skin irritation. Such increased concentrations may also result in the generation of more chlorine dioxide than is required.

Various methods have been described to limit or control the rate at which chlorine dioxide is produced in "acid generation" solutions. For instance, United States Patent No. Re. 31,779 (Alliger) describes a germicidal composition which comprises a water soluble chlorite, such as sodium chlorite, in combination with lactic acid. The particular composition possesses improved disinfectant properties, properties not attained by using the same composition but replacing the lactic acid with other acids such as phosphoric acid, acetic acid, sorbic acid, fumaric acid, sulfamic acid, succinic acid, boric acid, tannic acid, and citric acid. The germ killing composition is produced by contacting an acid material containing at least 15% by weight of lactic acid with sodium chlorite in aqueous media, the amount of lactic acid being sufficient to lower the pH of the aqueous media to less than about 7. The methods disclosed of disinfecting and sanitizing a germ-carrying substrate, such as skin, include either application of the germ-killing composition, or application of the reactants to provide *in situ* production thereof. Also, United States Patent No. 5,384,134 (Kross) describes acid induced generation of chlorine dioxide from a metal chlorite wherein the chlorite concentration is limited by the amount of available chlorous acid. In particular, the Kross patent describes a method for treating dermal disorders wherein a first gel, which comprises a metal chlorite, is mixed with a second gel, which comprises a protic acid. The chlorite ions present in such solution as chlorous acid purportedly comprise no more than about 15% by weight of the total chlorite ion concentration in the composition, and the mixture of the two gels purportedly generates chlorine dioxide over an extended time of up to 24 hours.

Other prior patents have purported to describe the use of "stabilized" chlorine dioxide as a means of chlorine dioxide generation. The term stabilized chlorine dioxide refers to various compositions in which the chlorine dioxide is believed to be held in solution in the form of a labile complex. The stabilization of chlorine dioxide by the use of perborates was disclosed in United States Patent No. 2,701,781 (de Guevara). According to the de Guevara patent, an antiseptic solution of stabilized chlorine dioxide can be formed from an aqueous solution of chlorine dioxide and an inorganic boron compound with the boron compound and the chlorine dioxide being present in the solution as a labile complex. The chlorine dioxide, fixed in this stable condition, is an essential ingredient of the antiseptic solution. The de Guevara patent discloses that the chlorine dioxide may be introduced into the compositions either by *in situ* generation or it may be generated externally and introduced into the solution, as by bubbling the chlorine dioxide gas into the aqueous solution. Various methods may be employed for the external production of the chlorine dioxide, such as reaction of sulfuric acid with potassium chlorate or the reaction of the chlorate with moist oxalic acid. Alternatively, chlorine dioxide can be generated in situ by reaction of potassium chlorate and sulfuric acid. Note that whether the chlorine dioxide is produced in situ or externally, it is essentially an acid induced liberation of the chlorine dioxide from potassium chlorate.

United States Patent No. 4,317,814 (Laso) describes stabilized chlorine dioxide preparations for treatment of burns in humans. Aqueous mixtures of perborate stabilized solutions of chlorine oxides, such as chlorine dioxide, in combination with glycerin are described for topical application to burned areas and may also be administered by oral application for treatment of bums.

The aqueous solutions of perborate stabilized chlorine oxides are disclosed as being prepared by mixing with water the following: sodium chlorite, sodium hypochlorite, hydrochloric acid, sulfuric acid, an inorganic perborate, and a peroxy compound, such as sodium perborate. Thus, the solutions prepared in accordance with the Laso patent contain chlorine dioxide, hypochlorite and peroxy compounds as strong oxidizing agents and appear to utilize acid activation of the chlorine dioxide. The Laso patent states that the methods disclosed therein resulted in an immediate subsidence of burn related pain in many cases, that healing was rapid and characterized by an absence of infection or contraction, and that the burn scars were smooth and resembled normal tissue, thus eliminating the need for plastic surgery in certain cases. However, long term storage and stability are issues with the aqueous solutions described in the above-identified Laso patent, because such mixtures tend to generate chlorine dioxide very quickly, thus diminishing the long term stability of such mixtures.

United States Patent No. 3,271,242 (McNicholas et al.) describes stabilized chlorine dioxide solutions which are formed by combining chlorine dioxide gas with an aqueous solution containing a peroxy compound, and subsequently heating the solution to a temperature which is high enough to drive off all free peroxide, but low enough not to destroy the chlorine dioxide. McNicholas et al. states that temperatures "much below" 70 degrees C are ineffective to drive off the free peroxide in the solution and that temperatures should not exceed 92 degrees C because at higher temperatures the chlorine dioxide will be driven off. McNicholas further states that, although not "entirely understood, " it was believed that heating of the solution to drive off free peroxide was necessary because any free hydrogen peroxide

allowed to remain in the solution would act as a leaching agent to release the chlorine dioxide from the solution.

ii. Antibiotic Preparations

Antibiotic compounds have also been commonly used for the therapeutic treatment of burns, wounds and skin infections. While antibiotics may provide an effective form of treatment, several dangers are often associated with the use of antibiotics in the clinical environment. These dangers may include but are not limited to: (1) changes in the normal flora of the body, with resulting "superinfection" due to overgrowth of antibiotic resistant organisms; (2) direct antibiotic toxicity, particularly with prolonged use which can result in damage to kidneys, liver and neural tissue depending upon the type of antibiotic; (3) development of antibiotic resistant microbial populations which defy further treatment by antibiotics.

B. Difficult-To-Treat Dermal Disorders Other Than Wounds, Burns, Abrasions and Infections

While even minor wounds and abscesses can be difficult to treat in certain patients and/or under certain conditions, there are well known dermal disorders such as psoriasis and dermal ulcerations, which present particular challenges for successful treatment.

i. Psoriasis

Psoriasis is a noncontagious skin disorder that most commonly appears as inflamed swollen skin lesions covered with silvery white scale. This most common type of psoriasis is called "plaque psoriasis". Psoriasis comes in many different variations and degrees of severity. Different types of psoriasis display characteristics such as pus-like blisters (pustular psoriasis), severe sloughing of the skin (erythrodermic psoriasis), drop-like dots (guttate psoriasis) and smooth inflamed lesions (inverse psoriasis).

The cause of psoriasis is not presently known, though it is generally accepted that it has a genetic

component, and it has recently been established that it is an autoimmune skin disorder. Approximately one in three people report a family history of psoriasis, but there is no pattern of inheritance. There are many cases in which children with no apparent family history of the disease will develop psoriasis.

The occurrence of psoriasis in any individual may depend on some precipitating event or "trigger factor." Examples of "trigger factors" believed to affect the occurrence of psoriasis include systemic infections such as strep throat, injury to the skin (the Koebner phenomenon), vaccinations, certain medications, and intramuscular injections or oral steroid medications. Once something triggers a person's genetic tendency to develop psoriasis, it is thought that in turn, the immune system triggers the excessive skin cell reproduction.

Skin cells are programmed to follow two possible programs: normal growth or wound healing. In a normal growth pattern, skin cells are created in the basal cell layer, and then move up through the epidermis to the stratum corneum, the outermost layer of the skin. Dead cells are shed from the skin at about the same rate as new cells are produced, maintaining a balance. This normal process takes about 28 days from cell birth to death. When skin is wounded, a wound healing program is triggered, also known as regenerative maturation. Cells are produced at a much faster rate, theoretically to replace and repair the wound. There is also an increased blood supply and localized inflammation. In many ways, psoriatic skin is similar to skin healing from a wound or reacting to a stimulus such as infection.

Lesional psoriasis is characterized by cell growth in the alternate growth program. Although there is no wound at a psoriatic lesion, skin cells (called "keratinocytes") behave as if there is. These keratinocytes switch from the normal growth program to regenerative maturation. Cells are created and pushed to

the surface in as little as 2-4 days, and the skin cannot shed the cells fast enough. The excessive skin cells build up and form elevated, scaly lesions. The white scale (called "plaque") that usually covers the lesion is composed of dead skin cells, and the redness of the lesion is caused by increased blood supply to the area of rapidly dividing skin cells.

Although there is no known cure for psoriasis, various treatments have been demonstrated to provide temporary relief in *some* patients. However, the effectiveness of the currently accepted treatments for psoriasis is subject to considerable individual variation. As a result, patients and their physicians may have to experiment and/or combine therapies in order to discover the regimen that is most effective. The currently available treatments for psoriasis are often administered in step-wise fashion. Step 1 treatments include a) topical medications (e.g., topical steroids, topical retinoids), b) systemic steroids, c) coal tar, d) anthralin, e) vitamin D3, and sunshine. Step 2 treatments include a) phototherapy (e.g, ultraviolet radiation), b) photochemotherapy (e.g., a combination of a topically applied radiation-activated agent followed by radiation to activate the agent) and c) combination therapy. Step 3 treatments include a) systemic drug therapies such as methotrexate, oral retinoids and cyclosporine and b) rotational therapy.

ii. Dermal Ulcerations

Dermal ulcerations are known to occur as a result of pressure, wear, or primary/secondary vascular disorders. Dermal ulcerations are generally classified according to their etiology, as follows:

a. Decubitus/Pressure Ulcers - A decubitus ulcer or pressure sore is a lesion caused by unrelieved pressure resulting in damage of the underlying tissue. Decubitus ulcers usually develop over a bony prominence such as the elbow or hip. The unrelieved pressure, along

with numerous contributing factors, leads to the skin breakdown and persistent ulcerations.

b. Venous Ulcers - Venous ulcers may result from trauma or develop after chronic venous insufficiency (CVI). In CVI, venous valves don't close completely, allowing blood to flow back from the deep venous system through the perforator veins into the superficialvenous system. Over time, the weight of this column of blood causes fluid and protein to exude into surrounding tissues, resulting in swollen, hyperpigmented ankles, tissue breakdown, and ulceration. Venous ulcers may be shallow or extend deep into muscle.

c. Arterial Ulcers - Leg ulcers also can develop in patients with arterial insufficiency caused by arterial vessel compression or obstruction, vessel wall changes, or chronic vasoconstriction. Smokers face an especially high risk of arterial disease because nicotine constricts arteries, encourages deposits of atherosclerotic plaque, and exacerbates inflammatory arterial disease (Buerger's disease) and vasoconstrictive disease (Raynaud's disease or phenomenon). Arterial ulcers, caused by trauma to an ischemic limb, can be very painful.

d. Diabetic Ulcers - Arterial insufficiency can be the cause of a nonhealing ulcer in a patient with diabetes. However, most diabetic ulcers result from diabetic neuropathy--because the patient can't feel pain in his foot, he's unaware of injuries, pressure from too-tight shoes, or repetitive stress that can lead to skin breakdown.

There remains a need in the art for the formulation and development of new disinfectants and topically applicable preparations for the treatment of dermal disorders, such as wounds, burns, abrasions, infections, ulcerations, psoriasis and acne.

C. **Contact Lens Soaking and Disinfection.**

Whenever a contact lens is removed from an eye, it should be placed in a soaking and disinfecting solution until it is worn again. soaking and disinfecting solutions have the following functions:

1. Aid in cleaning the lens of ocular secretions after the lens is removed form the eye;

2. To prevent eye infections by a bacterial contaminated lens; and

3. To maintain the state of hydrated equilibrium, which the lens achieves while it is being worn.

D. **Contact Lens Cleaning.**

During lens wear mucus material, lipids and proteins accumulate on contact lenses, making lens wear uncomfortable due to irritation, burning sensation,a nd redness. Accordingly, vision becomes blurry. To alleviate the discomforting problem, the soft or rigid contact lenses should be taken out of the eye, to be cleaned and disinfected regularly, suing an enzymatic cleaner and a disinfecting solution. One of the serious complications associated with soft lenses can be a Giant Papillary Conjunctivitis (GPC). It is believed to be that the occurrence of the giant papillary conjunctivitis is mostly due to an inflammatory reaction associated with soft contact lens complication. This is almost always caused by protein deposits on contact lenses. GPC produces symptoms ranging from asymptomatic to itching, upper eye-lid edema, red eye, mucoid discharge, progressive contact lens intolerance. The in-the-eye cleaner of the present invention effectively cleans the protein deposits and maintains corneal epithelial cells healthy by keeping the corneal surface from microbial infection as well as by supplying molecular oxygen. Thereby, it provides convenience and benefits to both soft and rigid contact lens wearers.

E. Treatment of Ophthalmic Disorders.

i. Dry Eye

Dry eye is a syndrome in which tear production is inadequate or tear composition is inappropriate to properly wet the cornea and conjunctiva. A variety of disorders of the ocular tears causes sensations of dryness of the eyes, discomfort of presence of a foreign object to occur in the eye. In most instances, the tear film loses its normal continuity and breaks up rapidly so that it cannot maintain its structure during the interval between spontaneous blinks. All of those tear abnormalities may have multiple causes. Perhaps the most common form of dry eye is due to a decreased aqueous component in the tears. Untreated dry eye can be further deteriorated to produce more severe epithelial erosion, strands of epithelial cells, and local dry spots on the cornea, which can be further complicated by microbial infection. In its mild form, however, a feeling of dryness and irritation of the eye can be solved with artificial tears. Thus, artificial tear solution which has a broad spectrum antimicrobial activity with corneal lubricating property, can provide not only comfort but also beneficial effects on recovery of damaged corneal surface.

ii. Allergic Conjunctivitis

Airborne or hand borne allergens usually produce allergic conjunctivitis due to IgE-mediated hypersensitivity reaction. It presents itching, tearing, dry and sticky eyes, including lid-swelling, conjunctival hyperemia, papillary reaction, chemosin, and ropy mucoid discharge. The presence of hyaluronic acid in the tear, which is included in the formulation of artificial tear, would protect corneal surface from contacting the allergens. The broad spectrum antimicrobial agent of the present invention keeps the corneal surface from bacterial infection and also maintains the corneal epithelial cells healthy by supplying molecular oxygen.

Thus, it provides beneficial effects on the eyes sensitive to allergens.

SUMMARY OF THE INVENTION

The present invention provides antimicrobial preparations (e.g., solutions, gels, ointments, creams, etc.) for disinfection of articles or surfaces (e.g., contact lenses, counter tops, etc.), antisepsis of skin or other body parts, prevention or minimization of scarring, and/or treatment or prophylaxis of dermal (i.e., skin or mucous membrane) disorders (e.g., wounds, burns, infections, cold sores, ulcerations, psoriasis, scar forming lesions, acne), and the treatment of ophthalmic disorders (e.g., dry eye, allergic conjunctivities, and wound healing). The antimicrobial preparations of this invention generally comprise from about 0.001% to about 0.20 by weight of a metal chlorite in combination with from 0.001% to 0.05% of a peroxy compound such as hydrogen peroxide. Additionally, the chlorite/peroxide preparations of the present invention may contain additional components such as polymeric lubricants and surfactants, and/or may be formulated in a polymeric drug delivery system or liposomal preparation. The chlorite/peroxide preparations of the present invention have broad antimicrobial activity, including for example activity against gram negative and gram positive bacteria, yeasts and fungi. Moreover, when applied or administered to treat dermal disorders (e.g.,wounds, burns, infections, ulcerations, acne and psoriasis), the chlorite/peroxide preparations of the present invention will not only prevent or lessen microbial infection, but will additionally provide oxygen to the affected tissue, aid in healing and deter scar formation.

Further in accordance with the invention, there are provided methods for disinfection of items (e.g., contact lenses) and methods for treatment of dermal disorders

(e.g.,wounds, burns, infections, ulcerations and psoriasis) by application or administration of a chlorite/peroxide preparation of the present invention. With respect to contact lens disinfecting solution, as well as product formulations that will clean contact lenses in the eye without removing the lenses from the eye for cleaning, the concentration of the metal chlorite is between about 0.002% to about 0.20%.

In addition, the invention includes product formulations shown to have efficacy in the treatment of dry eye, wound healing, and allergic conjunctivities.

Further in accordance with the invention, there are provided methods for deterring scar formation by application or administration of a chlorite/peroxide preparation of the present invention.

Further aspects and objects of the present invention will become apparent to those of skill in the art upon reading and understanding of the following detailed description and the examples set forth therein.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The following detailed description and examples are provided for the purpose of describing certain exemplary embodiments of the invention only, and are not intended to limit the scope of the invention in any way.

The present invention provides preparations which contain chlorite (e.g., a metal chlorite) in combination with a small amount of hydrogen peroxide in neutral aqueous (pH 6.8 - 7.8, preferably pH 7.0 - 7.4) solution. These preparations exhibit synergistic antimicrobial activity without generating chlorine dioxide during storage, thereby rendering the stability of these solutions acceptable for pharmaceutical use. For example, an aqueous solution containing 400 ppm chlorite plus 100 ppm hydrogen peroxide remains stable beyond 18 months at room temperature, and is effective to reduce *candida albicans* activity by 1.0 log within a 6 hrs of

challenge, even though the individual components of such solution are ineffective when applied separately at the same concentrations, to reduce *candida albicans* activity. Additionally, the hydrogen peroxide present within the chlorite/peroxide solutions of the present invention readily decomposes into molecular oxygen and water, upon contact with the peroxidase and catalase enzymes present in tissue and/or some body fluids. Such *in situ* generation of molecular oxygen contributes to cell vitality and enhances wound healing.

The chlorite/H_2O_2 solutions of the present invention are sufficiently stable to be formulated in combination with polymeric lubricants (non-ionic and/or anionic; e.g., HPMC, Methocel, CMC, hyaluronic acid, etc.) and/or in combination with block polymer based surfactants (e.g., pluronics). For example, an aqueous chlorite/hydrogen peroxide system can be formulated together with methocel or hyaluronic acid as a lubricant and pluronics as a surfactant for contact lens disinfectant solution (viscosity up to 50 cps at 25 degrees C) in an ophthalmically acceptable tonicity (e.g., osmolality of at least about 200 mOsmol/kg) and a buffer to maintain the pH of the formulation within an acceptable physiological range. The formulation of the contact lens disinfection solution, artificial tear solution, and in-eye cleaner solution, contains chlorite preferably from about 0.005 to about 0.06 weight/volume percent and hydrogen peroxide preferably from about 0.0002 to about 0.05 weight/volume percent. Again, the presence of hydrogen peroxide provides the beneficial oxygen molecule to the cornea upon contact with catalase in the tear.

A. Formulations

The chlorite/peroxide preparations of the present invention may be formulated in various ways, including liquid solutions, gels, ointments, creams, sprays, etc. Set forth herebelow are but a few examples of the types

of specific formulations which may be prepared in accordance with this invention.

i. A Stable Chlorite/Peroxide Liquid Solution

The following Formula 1 is a presently preferred formulation of a liquid chlorite/peroxide solution of the present invention:

FORMULA 1

Sodium Chlorite	0.005% - 0.10%
Hydrogen Peroxide . . .	0.005% -0.05%
Methocel A	0.05%-0.2%
Boric Acid	0.15%
Sodium Chloride	0.75%
Pluronic F-68/F-127 . .	0.1%
HCl or NaOH	Adjust pH 7.4
Purified water	Q.S. to volume

The chlorite/peroxide solutions of the present invention, such as the solution of the above-shown preferred formulation, may be used for a variety of medical and non-medical applications including but not necessarily limited to a) disinfection of articles and surfaces such as contact lenses, medical/dental instruments, counter tops, treatment tables, combs and brushes, etc; antisepsis of skin or body parts (e.g., a disinfectant hand wash, antiseptic facial scrub, etc.) and b) treatment or prophylaxix of dermal (i.e., skin or mucous membrane) disorders such as wounds, burns, infections, ulcerations, cold sores, psoriasis, acne, and c) deterrence or prevention of scar formation.

As pointed out earlier, the chlorite/hydrogen peroxide system of the present invention is sufficiently stable to be formulated in a polymeric gel form or in a paste form. Furthermore, such polymeric gel or paste formulation can contain polymers which delay or control the release of the chlorite/hydrogen peroxide (e.g., a sustained release delivery system). Such sustained release formulations provide outstanding benefits of increasing therapeutic index by maintaining the effective concentration of chlorite/H202 for a prolonged time on the injured sites, by preventing the injured sites from

external microbial contamination by forming a seal over the injured sites, and by providing oxygen molecule to the injured tissues. Unlike the conventional ointment, the polymeric gel provides a dry, clean, and comfortable coating on the injured sites upon application. Such gel formulations may contain polymeric drug delivery vehicles like hydroxypropyl methylcellulose (HPMC), methylcellulase (Methocel), hydroxyethylcellulose (HEC), hyaluronic acid, and carboxymethylcellulose (CMC), etc.

ii. A Stable Chlorite/Peroxide Gel

The following Formula 2 is a presently preferred formulation of a chlorite/peroxide gel of the present invention:

FORMULA 2

Sodium Chlorite	0.02% - 0.10%
Hydrogen Peroxide . . .	0.005% -0.05%
Methocel A	2.0%
Boric Acid	0.15%
Sodium Chloride	0.75%
Pluronic F-68/F-127 . .	0.1%
HCl or NaOH	Adjust pH 7.4
Purified water	Q.S. to volume

Any of the preparations of the present invention may be formulated for sustained release of the active components by forming liposomes of the preparing in accordance with well known liposomal forming techniques and/or by adding to the formulation a pharmaceutically acceptable and effective amount (e.g., typically 1-20 percent by weight) of a sustained release component such as a polymer matrix or one or more of the following:

a cellulose ester;
hydroxymethylpropyl cellulose;
methylhydroxyethyl cellulose;
hydroxypropyl cellulose;
hydroxyethyl cellulose;
carboxymethyl cellulose;
a salt of a cellulose ester;
cellulose acetate;
hydroxypropylmethyl cellulose phthalte;
methacrylic acid-methyl methacrylate copolymer;
methacrylic acid-ethyl acetate copolymer;
polyvinylpyrrolidone;
polyvinyl alcohol;
hyaluronic acid;

a phospholipid;
cholesterol;
a phospholipid having a neutral charge;
a phospholipid having a negative charge;
dipalmytoyl phoshatidyl choline;
dipalmytoyl phoshatidyl serine; and,
sodium salts thereof.

iii. A Stable Chlorite/Peroxide Ophthalmic Solution

The following Formula 3 is a presently preferred formulation of a chlorite/peroxide contact lens disinfecting solution for use in cleaning contact lenses residing in or out of the eye. The formulation additionally functions as a tear product for lubrication in dry-eye subjects.

FORMULA 3

Sodium Chlorite	*0.002% - 0.20%*
Hydrogen Peroxide . . .	*0.005% - 0.05%*
Hyaluronic Acid	*0.001% - 0.50%*
Boric Acid	*0.15%*
Sodium Chloride	*0.75%*
Pluronic 127	*0.05% - 2.0%*
HCl or NaOH	*Adjust pH to 7.4*
Purified Water	*Q.S. to Volume*

B. Examples of Therapeutic Applications

The following are specific examples of therapeutic applications of the chlorite/peroxide preparations of the present invention.

i. Example 1: Treatment of Psoriasis-No Crossover

A human patient having psoriasis plaques present on both arms is treated as follows:

- Twice daily application to plaques on the left arm only, of a chlorite/peroxide solution having the following formulation:

Sodium Chlorite	0.06%
Hydrogen Peroxide . . .	0.01%
HPMC	2.0%
Boric Acid	0.15%
HCl or NaOH	to adjust pH 7.4
Purified water	Q.S. to volume

- Twice daily application to plaques on the right arm only of a commercially available 0.1% triamcinolone acetonide cream.

The chlorite/peroxide treated psoriatic plaques on the right arm began to become less severe within 24 hours of beginning treatment and had substantially disappeared within 3 days of beginning treatment. However, the triamcinolone acetonide treated psoriatic plaques present on the left arm remained unchanged and inflamed during the two (2) week treatment period.

ii. Example 2: Treatment of Psoriasis-Crossover

A human patient having psoriasis plaques present on both arms is treated for two (2) weeks, as follows:

- Twice daily application to plaques on the left arm only, of a chlorite/peroxide solution having the following formulation:

Sodium Chlorite	0.06%
Hydrogen Peroxide . . .	0.01%
HPMC	2.0%
Boric Acid	0.15%
HCl or NaOH	to adjust pH 7.4
Purified water	Q.S. to volume/100%

- Twice daily application to plaques on the right arm only of a commercially available 0.1% triamcinolone acetonide cream.

The chlorite/peroxide treated psoriatic plaques on the right arm began to become less severe within 24 hours of beginning treatment and had substantially disappeared within 1 week of beginning treatment. However, the triamcinolone acetonide treated psoriatic plaques present on the left arm remained unchanged and inflamed during the two (2) week treatment period.

Beginning the day after the end of the initial two (2) week treatment period, and continuing for a second two (2) week treatment period, the patient was treated as follows:

- Twice daily application to plaques on the *left* arm only of the same commercially available 0.1% triamcinolone acetonide cream described hereabove in this example.
- Twice daily application to plaques on the *right* arm only, of the same chlorite/peroxide

sustained release gel described hereabove in this example.

Within 24 hours of commencing the second treatment period, the psoriatic lesions on the right arm began to subside. By day 3 and continuing through the end of the second two (2) week treatment period, the psoriatic lesions on the right arm had substantially disappeared.

iii. Example 3: Treatment of Cold Sores

A patient with painful, fluid-containing cold sores (i.e., chancre sores) on his lips was treated twice daily by application to the lips of a chlorite/peroxide preparation prepared in accordance with Formula 1 above.

Within 6 to 12 hours of the first application of the chlorite/peroxide preparation, the patient reported that the pain had subsided. Within 24 hours of the first application of the chlorite/peroxide preparation, the fluid contained within the cold sores had substantially dissipated and the cold sores appeared dry. Within 6 days of the first application of the chlorite/peroxide preparation the cold sores had substantially disappeared and the lips appeared normal, whereas cold sores of such severity typically require substantially longer than 6 days to completely disappear and heal.

iv. Example 4: Treatment of Venous Ulcer

A patient with a venous ulcer on the right leg of 3-4 cm diameter which had been present for 9-12 months was treated by twice daily application to the ulcer of gauze soaked with a chlorite/peroxide liquid solution prepared in accordance with Formula 1 above.

Within 3 days after commencement of treatment the ulcer appeared clean and dry. Within 14 days of the commencement of treatment the ulcer began to decrease in size and healthy new tissue was observed about its periphery. At 35 days after commencement of treatment, the ulcer had completely healed, without scarring, and the area where the ulcer had been located was free of pain.

v. Example 5: Treatment of Diabetic Decubitus Ulcer

A non-ambulatory, diabetic patient with decubitus ulcers on both legs and some toes, of 12-18 month duration, was treated by daily application of clean, sterile gauze to the ulcers and saturation of each gauze, 3 times each day, with a liquid chlorite/peroxide solution prepared in accordance with Formula 1 above. Within 4 to 7 days of commencing the chlorite/hydrogen peroxide treatments the ulcers began to appear less inflamed, clean and dry. About 7 to 10 days after commencement of the chlorite/hydrogen peroxide treatment, granulation tissue began to form within the ulcers. Within 12 to 14 days, re-epithelialization was observed to have begun within the ulcerated areas except for one toe ulcer which had been particularly sever and had permeated to the bone of the toe. Within 30 to 45 days of the commencement of treatment, all of the ulcers except for the severe toe ulcer had completely closed and re-epithelialized, without irregular scar formation. Also, at 30 to 45 days after the commencement of treatment, the toe ulcer had also become substantially smaller (but was not completely closed) and the patient was able to walk. The liquid and or gel formulations of the present invention, such as Formulas 1 and 2 above, may also be applied topically to prevent scar formation due to wounds, burns, acne, infections, trauma, surgical incision, or any other scar-forming lesion or disorder.

vi. Example 6:

a. Treatment of Dry Eye Conditions

Subjects with dry eye condition have itchy and scratchy eyes. In extreme cases, the subjects have more serious problems that can interfere with health maintenance. Subjects were treated with a preferred tear product of the following formulation:

Sodium Chlorite	0.005% - 0.02%
Hydrogen Peroxide . . .	0.01%
Methylcellulose A4M . .	0.075%
Hyaluronic Acid	0.10% - 0.125%

Boric Acid	0.15%
Sodium Chloride, USP .	0.75%
Pluronic 127	0.10%
HCl or NaOH	Adjust pH to 7.4
Purified Water	Q.S. to Volume

Testing of dry eye subjects with rose bengal stain or fluorescein gives a good indication regarding the condition of the corneal epithelial health, while rose bengal staining provides a good indication of the number of dead epithelial cells on the cornea as well as conjunctiva.

Two subjects with dry eye condition were tested with rose bengal stain, and the quantitative staining to the cornea and conjunctiva was documented by photographs. the subjects started using the above preferred tear product at a dosage of two drops three times per day. At the end of two weeks, the two subjects were tested with rose bengal stain and the level of staining was quantitatively documented by photography. The results showed a 50% to 70% reduction in rose bengal staining, which clearly indicates that the preferred tear formulation was ameliorating the corneal and conjunctival cells from dying.

In addition to an objective determination of the health of the epithelial cells, the two subjects were tested subjectively regarding the safety and efficacy of the preferred tear product. First of all, slit-lamp biomicroscopy of the subjects during the two-week treatment period did not show any redness, irritation, inflammation, or other signs of discomfort. Second, the subjects indicated that the application of the tear product completely removed symptoms of redness, itching, scratching, pain, and dryness due to dry eye while providing lubrication that lasted for several hours. It is therefore evident that the tear product exhibits both safety and efficacy in the treatment of dry eye. As is further recognized in view of the foregoing antimicrobial activity of such compositions, the tear product will also

have efficacy in enhancing wound healing within the eye such as after surgery where bacterial infections are to be avoided.

b. Treatment of Allergic Conjunctivities

In addition to treating dry eye condition with the above preferred tear product, the product was also tested in the treatment of conditions from allergic conjunctivities. In particular, two subjects suffering from allergic conjunctivities including itchy, scratchy eyes with constant tearing applied two drops of the product three times per day. This dosage resulted in the disappearance of the symptoms.

C. Examples of Contact Lens Cleansing

i. Example 1: Soaking, **Cleaning and Disinfecting**

The following formulation is a preferred disinfecting solution applicable to the cleaning of contact lenses by conventional soaking.

Sodium Chlorite	0.05%
Hydrogen Peroxide . . .	0.01%
Methylcellulose A4M . .	0.075%
Hyaluronic Acid	0.05% - 0.10%
Boric Acid	0.15%
Pluronic 127	0.25% - 0.50%
Sodium Chloride USP . .	0.75%
HCl or NaOH	Adjust pH to 7.4
Purified Water	Q.S. to Volume

Six subjects using soft hydrophilic contact lenses soaked the lenses in the above disinfecting solution and then placed the lenses directly into the eyes. Soaking was performed nightly or on an as-needed basis. All six subjects reported that the lenses felt very comfortable, and that no adverse effects (e.g. burning, stinging, redness, pain) were experienced. Additionally, the solution extended the comfort and clean condition of the lenses for several weeks beyond such extension experienced with other commercially available disinfecting solutions.

The disinfecting solution can be used with soft hydrophilic lenses of varying water content (e.g. 38% to 75%), as well as with silicone acrylate rigid gas

permeable lenses. Cycling studies of soft lenses soaked daily in the solution for 30 days showed no damage or change in the physical and chemical characteristics of the lenses. Eye comfort, as earlier noted, is achieved through non-binding and non-accumulating of preservative in soft or rigid gas permeable lenses, while such binding and accumulation can be found in certain currently commercially available formulations to cause irritation and discomfort.

ii. Example 2: Cleaning While Wearing

The following formulation is a preferred disinfecting in-eye solution applicable to the cleaning of contact lenses while they are being worn by introducing the solution into the eye:

Sodium Chlorite	0.02%
Hydrogen Peroxide . . .	0.01%
Methylcellulose A4M . .	0.075%
Hyaluronic Acid	0.075% - 0.10%
Boric Acid	0.15%
Sodium Chloride USP . .	0.75%
Pluronic 127	0.75%
HCl or NaOH	Adjust pH to 7.4
Purified Water	Q.S. to Volume

Four subjects applied two drops of the above in-eye solution three times per day for 30 days to contact lenses while being worn. Examinations of all of the subjects showed no irritation, burning, stinging, or adverse effects of any kind. These subjects further reported that the solution felt soothing and lubricating.

Two subjects were involved in a comparative study where, first of all, they wore ACUVUE disposable lenses continuously for two weeks with occasional removal and cleaning with commercially available cleaning solutions followed with a saline rinse. After 14 days, the lenses became very gritty and uncomfortable, and were discarded. Second, the two subjects started with new ACUVUE lenses and practiced daily application of the present in-eye solution three times per day without removing or touching the lenses. These subjects were able to wear the lenses for three to four weeks before replacement.

Additionally, the inconvenience of cleaning the lenses outside the eye was completely eliminated, as was the risk of lens loss, tearing, or contamination. It is therefore evident that the present in-eye cleaning solution provides cleansing efficacy as well as convenience.

It will be appreciated by those skilled in the art, that the invention has been described hereabove with reference to certain examples and specific embodiments. However, these are not the only examples and embodiments in which the invention may be practiced. Indeed, various modifications may be made to the above-described examples and embodiments without departing from the intended spirit and scope of the present invention, and it is intended that all such modifications be included within the scope of the following claims.

What is claimed is:

1. A preparation for a) disinfection, b) polymeric lubricant preservation, c) antisepsis, d) treatment of wounds, burns, infections and disorders of the skin or mucous membranes and d) prevention or deterrence of scar formation, said preparation comprising:

approximately 0.02-0.20 percent by weight of chlorite; and,

approximately 0.005-0.01 percent by weight of a peroxy compound.

2. A preparation according to Claim 1 wherein the chlorite is present as a metal chlorite.

3. A preparation according to Claim 2 wherein the metal chlorite is selected from the group of metal chlorites consisting of:

sodium chlorite;

potassium chlorite;

calcium chlorite; and,

magnesium chlorite.

4. A preparation according to Claim 1 wherein the peroxy compound is hydrogen peroxide.

5. A liquid preparation according to Claim 1 comprising:

Sodium Chlorite . . . . 0.005% - 0.10%;

Hydrogen Peroxide . . . 0.005% -0.01%;

Methocel A 0.05%-0.2%;

Boric Acid 0.15%;

Sodium Chloride 0.75%;

Pluronic F-68/F-127 . . 0.05% - 2.0%;

HCl or NaOH . . . . . to adjust pH to about 7.4; and,

Purified water . . . . Q.S. to volume.

6. A gel preparation according to Claim 1 comprising:

Sodium Chlorite . . . . 0.005% - 0.10%;

Hydrogen Peroxide . . . 0.005% -0.01%;

Methocel A 0.05%-2.0%;

Boric Acid 0.15%;
Sodium Chloride 0.75%;
Pluronic F-68/F-127 . . 0.05% - 2.0%;
HCl or NaOH . . . . . Adjust pH 7.4; and
Purified water . . . . Q.S. to volume;

7. A sustained release preparation according to Claim 1 wherein said preparation further comprises:

a sustained delivery component which limits the rate at which the chlorite becomes available for generation of chlorine dioxide and hydrogen peroxide becomes available for generation of oxygen.

8. A sustained release preparation according to Claim 7, wherein the sustained delivery component comprises a polymer matrix.

9. A sustained release preparation according to Claim 7, wherein the sustained delivery component comprises a liposome.

10. A sustained release preparation according to Claim 7, wherein the sustained delivery component is selected from the group consisting of:

a cellulose ester;
hydroxymethylpropyl cellulose;
methylhydroxyethyl cellulose;
hydroxypropyl cellulose;
hydroxyethyl cellulose;
carboxymethyl cellulose;
a salt of a cellulose ester;
cellulose acetate;
hydroxypropylmethyl cellulose phthalte;
methacrylic acid-methyl methacrylate copolymer;
methacrylic acid-ethyl acetate copolymer;
polyvinylpyrrolidone;
polyvinyl alcohol;
hyaluronic acid;
a phospholipid;
cholesterol;

a phospholipid having a neutral charge;
a phospholipid having a negative charge;
dipalmytoyl phoshatidyl choline;
dipalmytoyl phoshatidyl serine; and,
sodium salts thereof.

11. A sustained release preparation according to Claim 7, wherein the sustained delivery component comprises 1-20 percent by weight of the preparation.

12. A preparation according to Claim 1 which is a liquid.

13. A preparation according to Claim 1 which is a gel.

14. A preparation according to Claim 1 which is a cream.

15. A preparation according to Claim 1 which is an ointment.

16. An ophthalmic preparation for a) disinfection of contact lenses and treatment of dry eye condition, ophthalmic wound healing, allergic conjunctivities, said preparation comprising:

approximately 0.002-0.20 percent by weight of a chlorite; and,

approximately 0.005-0.05 percent by weight of a peroxy compound.

17. A preparation according to Claim 16 wherein the chlorite is present as a metal chlorite.

18. A preparation according to Claim 17 wherein the metal chlorite is selected from the group of metal chlorites consisting of:

sodium chlorite;
potassium chlorite;
calcium chlorite; and,
magnesium chlorite.

19. A preparation according to Claim 16 wherein the peroxy compound is hydrogen peroxide.

20. A liquid preparation according to Claim 16 comprising:

Sodium Chlorite . . . . 0.002% - 0.20%;
Hydrogen Peroxide . . . 0.005% - 0.05%;
Hyaluronic Acid . . . . 0.001% - 0.50%
Boric Acid 0.15%;
Sodium Chloride 0.75%;
Pluronic 127 . . . . . 0.10% - 2.0%;
HCl or NaOH . . . . . to adjust pH to about 7.4; and,
Purified water . . . . Q.S. to volume.

21. A method for treating a disorder present on an affected area of the skin or mucous membrane of a mammalian patient and for preventing scar formation, said method comprising the step of:

a) contacting with the affected area a preparation which comprises:

approximately 0.005-0.10 percent by weight of chlorite; and,

approximately 0.005-0.01 percent by weight of a peroxy compound.

22. The method of Claim 21 wherein the chlorite present in the solution in Step a comprises a metal chlorite.

23. The method of Claim 22 wherein the metal chlorite contained in the preparation used in Step a is selected from the group of metal chlorites consisting of:

sodium chlorite;
potassium chlorite;
magnesium chlorite; and,
calcium chlorite.

24. The method of Claim 21 wherein the peroxy compound contained in the preparation used in Step a is hydrogen peroxide.

25. A method according to Claim 21 wherein the preparation is a liquid comprising:

Sodium Chlorite . . . . 0.005% - 0.10%;
Hydrogen Peroxide . . . 0.005% -0.01%;
Methocel A 0.05%-0.2%;

Boric Acid 0.15%;
Sodium Chloride 0.75%;
Pluronic F-68/F-127 . . 0.1%;
HCl or NaOH . . . . . to adjust pH to about 7.4; and,
Purified water . . . . Q.S. to volume.

26. A method according to Claim 21 wherein the preparation is a sustained release preparation which further comprises:

a sustained delivery component which limits the rate at which the chlorite becomes available for generation of chlorine dioxide.

27. A method according to Claim 26 wherein the sustained release component comprises a polymer matrix.

28. A method according to Claim 26 wherein the sustained release component comprises a liposome.

29. A method according to Claim 26 wherein the sustained release component is selected from the group consisting of:

a cellulose ester;
hydroxymethylpropyl cellulose;
methylhydroxyethyl cellulose;
hydroxypropyl cellulose;
hydroxyethyl cellulose;
carboxymethyl cellulose;
a salt of a cellulose ester;
cellulose acetate;
hydroxypropylmethyl cellulose phthalte;
methacrylic acid-methyl methacrylate copolymer;
methacrylic acid-ethyl acetate copolymer;
polyvinylpyrrolidone;
polyvinyl alcohol;
hyaluronic acid;
a phospholipid;
cholesterol;
a phospholipid having a neutral charge;
a phospholipid having a negative charge;

dipalmytoyl phoshatidyl choline;
dipalmytoyl phoshatidyl serine; and,
sodium salts thereof.

30. A method according to Claim 26 wherein the sustained release component comprises 1-20 percent by weight of the preparation.

31. A method according to Claim 21 wherein the preparation is a liquid.

32. A method according to Claim 21 wherein the preparation is a gel.

33. A method according to Claim 21 wherein the preparation is a cream.

34. A method according to Claim 21 wherein the preparation is an ointment.

35. A method of cleaning contact lenses residing in or out of eyes, said method comprising the application to the lenses of an effective amount of a disinfecting preparation comprising from about 0.002-0.20 percent by weight of a chlorite and about 0.005-0.05 percent by weight of a peroxy compound.

36. A method according to Claim 35 wherein the chlorite comprises a metal chlorite.

37. A method according to Claim 36 wherein the metal chlorite is selected from the group of metal chlorites consisting of:
sodium chlorite;
potassium chlorite;
magnesium chlorite; and,
calcium chlorite.

38. A method according to Claim 37 wherein the peroxy compound is a hydrogen peroxide.

39. A method according to Claim 35 wherein the preparation comprises:

Sodium Chlorite	0.002% - 0.20%
Hydrogen Peroxide . . .	0.005% - 0.05%;
Hyaluronic Acid	0.001% - 0.50%
Boric Acid	0.15%;

Sodium Chloride 0.75%;
Pluronic 127 . . . . . 0.10% - 2.0%;
HCl or NaOH . . . . . to adjust pH to about 7.4; and,
Purified water . . . . Q.S. to volume.

40. A method of treating a dry eye condition, ophthalmic wound healing, and allergic conjunctivities of eyes, said method comprising the application to the eyes of an effective amount of an ophthalmic preparation comprising from about 0.002-0.20 percent by weight of a chlorite and about 0.005-0.05 percent by weight of a peroxy compound.

41. A method according to Claim 40 wherein the chlorite comprises a metal chlorite.

42. A method according to Claim 41 wherein the metal chlorite is selected from the group of metal chlorites consisting of:
sodium chlorite;
potassium chlorite;
magnesium chlorite; and,
calcium chlorite.

43. A method according to Claim 42 wherein the peroxy compound is hydrogen peroxide.

44. A method according to Claim 40 wherein the preparation comprises:
Sodium Chlorite . . . . 0.002% - 0.20%
Hydrogen Peroxide . . . 0.005% - 0.05%;
Hyaluronic Acid . . . . 0.001% - 0.50%
Boric Acid 0.15%;
Sodium Chloride 0.75%;
Pluronic 127 . . . . . 0.10% - 2.0%;
HCl or NaOH . . . . . to adjust pH to about 7.4; and
Purified water . . . . Q.S. to volume.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/23291

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/127, 33/40; A01N 25/00, 59/08, 59/14
US CL : 424/405, 420, 450, 484, 486, 487, 488, 450, 613, 614, 615, 616, 661, 665; 514/553, 557, 964, 875, 970

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/405, 420, 450, 484, 486, 487, 488, 450, 613, 614, 615, 616, 661, 665; 514/553, 557, 964, 875, 970

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,317,814 A (LASO) 02 March 1982, column 3, lines 20-40.	1-8, 10-27, 29-44
Y	US 4,891,216 A (KROSS et al.) 02 January 1990, column 2, lines 54-60, column 3, lines 1-39, column 4, lines 3-9, 11-18, 32, 33, column 5, lines 15, 16, column 7, lines 40-68, column 8, lines 1-3.	1-8, 10-27, 29-44
Y	US 3,585,147 A (GORDON) 15 June 1971, column 2, lines 54-64, column 3, lines 26-29, 38-40, 49-55, 59-75, column 4, lines 1, 2.	1-8, 10-27, 29-44
Y	US 4,574,084 A (BERGER) 04 March 1986, column 2, lines 24-68, column 3, lines 1-3, 46-53, 60-63, column 7, lines 61-68, column 8, lines 1-58.	1-8, 10-27, 29-44
Y	US 5,306,440 A (RIPLEY et al.) 26 April 1994, column 9, lines 3-12, 67, column 10, lines 1-29.	1-8, 10-27, 29-44
Y	US 5,736,165 A (RIPLEY et al.) 07 April 1998, column 2, lines 1-58, column 3, lines 28-49, column 4, lines 64-68, column 5, lines 1-64, column 7, lines 20-68.	1-8, 10-27, 29-44
Y,P	US 5,855,922 A (DANNER et al.) 05 January 1999, see claims 1-8.	1-8, 10-27, 29-44
A	US 4,670,185 A (FUJIWARA et al.) 02 June 1987, column 1, lines 22-31.	9, 28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1999 (23.11.1999)	08 FEB 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Frank Choi Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US99/23291

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ **Claim Nos.:**
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ **Claim Nos.:**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ **Claim Nos.:**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/23291

Continuation of B. FIELDS SEARCHED Item 3: APS, STN/CAS

search terms: chlorite, peracid, percarboxylic acid, peroxy acid, perborate, persulfate, hydrogen peroxide, lipid, phospholipid, vesicle, methocel, sodium chloride, pluronic, hydrochloric acid, hydrogem peroxide, polyoxyalkylene ether, methylcellulose, micelle, liposome, gel, cream, ointment, cholesterol